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Translational research in acute lung injury and pulmonary fibrosis attenuating endogenous Fgfr2b ligands during bleomycin-induced lung fibrosis does not compromise murine lung repair

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Abstract

© 2015 the American Physiological Society Fibroblast growth factors (Fgfs) mediate organ repair. Lung epithelial cell overexpression of Fgf10 postbleomycin injury is both protective and therapeutic, characterized by increased survival and attenuated fibrosis. Exogenous administration of FGF7 (palifermin) also showed prophylactic survival benefits in mice. The role of endogenous Fgfr2b ligands on bleomycin-induced lung fibrosis is still elusive. This study reports the expression of endogenous Fgfr2b ligands, receptors, and signaling targets in wild-type mice following bleomycin lung injury. In addition, the impact of attenuating endogenous Fgfr2b-ligands following bleomycin-induced fibrosis was tested by using a doxycycline (dox)-based inducible, soluble, dominant-negative form of the Fgfr2b receptor. Double-transgenic (DTG) Rosa26$^{rtTA/+}$;tet(O)solFgfr2b mice were validated for the expression and activity of soluble Fgfr2b (failure to regenerate maxillary incisors, attenuated recombinant FGF7 signal in the lung). As previously reported, no defects in lung morphometry were detected in DTG (+dox) mice exposed from postnatal days (PN) 1 through PN105. Female single-transgenic (STG) and DTG mice were subjected to various levels of bleomycin injury (1.0, 2.0, and 3.0 U/kg). Fgfr2b ligands were attenuated either throughout injury (days 0-11; days 0-28) or during later stages (days 6-28 and 14-28). No significant changes in survival, weight, lung function, confluent areas of fibrosis, or hydroxyproline deposition were detected in DTG mice. These results indicate that endogenous Fgfr2b ligands do not significantly protect against bleomycin injury, nor do they expedite the resolution of bleomycin-induced lung injury in mice.

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